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(54) Adhesion prevention and an endoscopic insufflation system therefor

(57) The invention relates to an anoxemia preventing compound for the manufacture of a medicament for preventing adhesion formation.

The invention further relates to an endoscopic insufflation system comprising gas supplying means for a insufflation line, wherein the supplying means are designed to supply gas mixtures comprising O_2.

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Description

The present invention relates to adhesion prevention by adhesion preventing compounds, products and/or an endoscopic insufflation system therefor.

Adhesion formation is a major problem following surgical procedures and is a frequent cause of postoperative pain and of infertility. Adhesions are the major cause of intestinal obstruction and it is estimated that following an intra-abdominal procedure, adhesions occur in some 50 to 80 percent of patients.

The mechanism of adhesion formation can be summarized as follows: a trauma of the peritoneal lining is rapidly followed by an inflammatory reaction; exudation of plasma, and deposition of a fibrin matrix. Subsequently the lesion is healed by the degradation of the fibrin deposition, and by proliferation of the mesenchymal lining of the peritoneum. If the repair process is not completed within a few days, fibroblast proliferation starts which ultimately will end in collagen deposition and adhesion formation. Key players in this process are in particular fibrin and fibrinolysis, macrophages and their secretion products such as growth hormones and cytokines, and obviously the epithelial repair process. From this repair process it results that adhesion formation is largely independent from the extent of the trauma.

Prevention of adhesion formation has been attempted mechanically and by modulating the inflammatory reaction. Mechanical adhesion prevention has been attempted by barrier methods and by the instillation of viscous fluids at the end of surgery keeping the surfaces separated, or recently by coating the surfaces by biodegradable gels.

These known approaches have been only moderately succesful.

Surprisingly, the applicant found that anoxemia is a major cause and/or cofactor of adhesion formation. The invention relates in particular to the use of an anoxemia preventing compound for the manufacture of a medicament for preventing adhesion formation.

These local or systemic administered medicaments according to the invention reduce adhesion formation by decreasing anoxemia in particular of the peritonial lining or the consequences of peritoneal anoxemia.

Hereunder mechanisms and drugs are highlighted which are proven to be relevant to reduce/prevent adhesion formation. These drugs have hitherto not been used in adhesion prevention, at least not in the concept of prevention of ischemia and/or anoxemia and/or of the consequences of ischemia and/or anoxemia.

The damage caused by ischemia and/or anoxemia has been investigated to occur during the period of ischemia and/or anoxemia itself, and during the reperfusion period. The mechanisms which are recognized to be involved are Ca channels, kalium efflux, free oxygen radicals, expression of a series of proteins such as VEGF (a potent angiogenic factor), other cytokines which are leucocyte attractants and heat shock proteins.

These drugs can be applied either systemically, or by local instillation during surgery, or by the prolonged administration intraperitoneally postoperatively, preferably locally e.g. by miniosmotic pumps. Experiments have shown, that this is feasible, that the local administration has the advantage that much higher concentrations of active drugs can be obtained, and that the administration for 24 to 36 hours postoperatively is sufficient.

Considering the knowledge of prevention of ischemia and/or anoxemia and/or of the consequences of ischemia and/or anoxemia the time course of administration of these drugs to prevent adhesions will obviously be different from those actually used.

Together with the hereunder explained oxygen/CO_2 pneumoperitoneum or independently at least the following mechanisms and/or drugs/mechanisms can be used for the prevention of adhesions:

- drugs to prevent anoxemia or the consequences thereof can also be administered, continuously or intermittently in the insufflation gas or mixture as an aerosol. For this purpose all drugs as mentioned later can be used;
- activation of potassium channels;
- modulation of macrophage activation and leucocyte attraction through cytokines, or their inhibitors e.g. IL8, IL6, IL1;
- the effect of VEGF expression, a direct consequence of anoxemia, will be blocked by antibodies or other inhibitors;
- indomethacin, which can inhibit the membrane lipid peroxidation products following anoxemia;
- prostaglandin E1 was shown to reduce the consequences of ischemia and/or anoxemia in the liver;
- allopurinol was shown to reduce the consequences of ischemia and/or anoxemia in the kuppfer cells of the liver through an effect on xanthine-oxidase;
- calcium channel blockers, free radical scavengers, lipid peroxysomes, and pregnatrienes;
- calcium antagonists;
- prevention of hypoxia associated stress proteins;
- acidosis can prevent reperfusion damage;
- MP, dopamine and ATP-MgCl2 administered following the anoxemia as demonstrated for the liver.

The amount of these active ingredients of the present invention may vary depending on the formulation, but it is usually from 0.1 to 50% by weight irrespective of the manner of administration. The dose is determined taken into consideration the age, sex, and syptom of disease of the subject, the desired therapeutic effect, the period of administration, etc. However preferably a daily dose of the active ingredient is from 0.05 to 100 mg for an adult.

The invention relates also to a novel endoscopic

insufflation system with supplying means for O_2.

Endoscopy also called minimal access surgery has become widely used over the last years because of clearcut advantages of a decreased postoperative morbidity, less pain and a shorter hospitalization. These procedures require by means of an insufflation system or an irrigation system a distension to permit visualization.

Endoscopic surgery uses, at present, almost exclusively pure carbon dioxide gas (CO_2). A standard lesion induced either by CO_2 laser (superficial lesion) or by monopolar, or bipolar coagulation, (deeper lesion) cause more adhesions when the duration of the pneumoperitoneum is longer. The amount of adhesions increase with time, at least up to 2 hours. All existing insufflation systems are designed to control gas flow for pure carbon dioxide gas. Since CO_2 is highly soluble in water, this gas has almost uniformly been used to induce the pneumoperitoneum, for safety reasons. In cases of accidental gas embolism the solubility in water and the exchange capacity in the lungs is estimated to be possibly of crucial life saving importance.

CO_2 irritates the peritoneum, as evidenced by the pain when insufflated without anaesthesia, and by the shoulder pain following endoscopic procedures. This can be explained by the pH changes caused by CO_2.

The endoscopic insufflation system according to the invention comprises gas supplying means for a insufflation line, wherein the supplying means are designed to supply gas mixtures comprising O_2 and in particular gas mixtures of O_2/CO_2. Supprisingly it was found that O_2 comprising gas mixtures reduce adhesion formation. Other O_2 gas mixtures, for example with N_2O or Helium can also be used as insufflation gases with preventing adhesion formation characteristics according to the invention.

For intra-abdominal endoscopy, the distension medium is generally a gas whereas for organs such as a uterus, both gases and fluids can be used.

In a series of experiments in rabbits and mice it was recently shown that CO_2 is an independent adhesiogenic factor. CO_2 causes not only pH changes. Taking into account the relative pressures, it was found that the peritoneal lining was anoxic during the pneumoperitoneum and that this was a direct cause of cell damage and adhesion formation.

The present invention shows that the presence of O_2 diminished the adhesion formation. This was experimentally proven by the administration of 1,2.5,5;10 and 20% of oxygen together with the CO_2. In these experiments, exposure of 60 min of pure CO_2 increased the adhesion scores 4 fold in comparison with an exposure of 10 min. From a final concentration of 5% oxygen onwards, this adhesiogenic effect of CO_2 was completely abolished. Also visually the appearance of the lesions following pure CO_2 and following a CO_2/oxygen mixture was obviously different, the latter looking much healthier.

These above mentioned experiments demonstrate clearly that prevention of anoxemia reduces adhesion formation, which principle is used as a basis in developing an insufflation system which delivers a controlled O_2/CO_2 mixture.

An endoscopic insufflation system according to the invention is preferably provided with means for moistening the insufflation gas. For example by means for a sprinkler device.

Drying of peritoneal surfaces has been considered a cofactor in adhesion formation. For this reason as a single measure or together with the prevention of anoxemia using oxygen in the insufflation gas or using drugs to prevent anoxemia or the consequences thereof, it is important that the insufflated gas is moistened in order to prevent dehydration of the peritoneal surfaces. Instead of moistening the insufflated gas, a sprinkler system has been devised which intermittently sprays the abdominal cavity. This sprinkler device can be attached to any canula, or preferably to the endoscope: under high pressure a small volume of irrigating fluid is intermittently and automatically sprayed in all directions of the abdominal cavity.

The insufflation system according to the invention will be further illustrated hereunder, on the basis of a number of non limitative embodiments, and with reference to the annexed drawing, wherein figures 1 and 2 are extensively schematised drawings of control means of an insufflator system according to the invention.

During endoscopy or endoscopic surgery, the abdominal cavity generally is or can intentionally be irrigated with a solution such as Ringers lactate or any other physiologic solution . The invention that anoxemia or the consequences thereof should be prevented, will use medicated irrigation fluids. For this purpose any of the substances as described can be used, in order to recuce that anoxemia or the consequences thereof, already during surgery. Alternatively, at the beginning of the surgery, the peritoneal surfaces can be coated with a biodegradable gel, which will prevent the direct contact of CO_2 with the peritoneal surface and thus changes in pH and/or anoxemia.

First an overview is given of possible technical solutions to the problem of applying carbon dioxide-oxygen (CO_2/O_2) gas mixtures during endoscopical surgery.

The requirements of such an insufflation system according to the invention are those of a pure CO_2 insufflator with additionally:

- means for controlling the ratio of carbon dioxide-oxygen, which ratio is preferably controlled independently from the gas flow;
- means for adjusting the ratio of carbon dioxide-oxygen during the endoscopical surgery (e.g. start the operation with pure carbon dioxide and after a while switch to a 50% oxygen mixture);
- flow control means for the carbon dioxide-oxygen gas mixture.

The initiation of the pneumoperitoneum should preferably be done at insufflation pressures below 15 mm Hg and at a flow rate of less than 1L/min. Once the pneumoperitoneum established, the most important factor is the intra-abdominal pressure which should not exceed 30 mm of Hg. The flow rate becomes relatively unimportant.

A first embodiment of an insufflation system according to the invention makes use of fixed gas mixtures. One can perform endoscopical surgery using carbon dioxide-oxygen gas mixtures using containers of premixed gases. It is obvious that this solution offers total independability of CO_2-O_2 ratio from gas flow. Flow control can be obtained using existing equipment. This embodiment has the advantage of its simplicity. The only extra equipment needed are some containers with mixtures of carbon dioxide gas and oxygen with different CO_2-O_2 ratios and a valve to switch from one mixture to another. This valve can be placed before the gas inlet of existing equipment, or it can be integrated into an apparatus for gas flow control. The valve can be pure mechanical, or electromechanical.

An important limitation of this first embodiment is the fact that it is impossible to continuously vary the carbon-dioxide-oxygen ratio during an endoscopical operation. Only a number of fixed ratios can be used during an operation. Hereunder are two other embodiments proposed, which can overcome this limitation.

Figure 1 gives a schematic overview of an open loop control system for mixing carbon dioxide and oxygen in a predefined ratio.

The proposed solution consists of a buffer volume 6 and a controller unit 7. The two (one for oxygen, one for carbon dioxide) gas inlets are equipped with electromechanical valves 4 and 5.

A periodically opening of the valves 4 and 5, makes it possible to mix the two gases in the buffer volume 6. If one makes sure that the opening times of the valves are rather small, or the incoming gas flow is rather small or the buffer volume 6 is rather large, then the pressure in the buffer volume 6 will remain rather constant during one period.

In short, the increase in pressure in the buffer volume 6 during one period, can be neglected for small periods, large buffer volumes or small incoming gas flows. By consequence, if these conditions are met, the gas flow in the two gas inlets can be considered equal and the ratio of the two gases in the buffer volume 6 will be the same as the ratio of the opening times of the two valves.

Since no feedback is provided in this solution, some extra measures are necessary to make sure gas always flows in the buffer volume 6 through the valves 3 and 4. This can be achieved by providing the pressure sensors 1, 2 and 3. The controller unit 7 may only periodically open valves if the pressure at sensor 3 is smaller than the pressure at the sensors 1 and 2. The controller unit must issue a warning to the user if the pressure at sensors 1 or 2 drops below some predefined value. In order to compensate for slight differences in input pressure between 1 and 2 (and by consequence, differences in incoming gas flow), the controller must always maintain a predefined pressure difference between the buffer volume 6 and the incoming gas flows.

This embodiment has the advantage of flexibility over the previous one. By varying the ratio of opening times of the valves 4 and 5 any carbon dioxide-oxygen ratio can be achieved. Response will not be immediate, since the buffer volume 6 will introduce a delay.

This embodiment can be placed before the gas inlet of existing equipment for flow control, or integrated in new equipment for flow control.

This embodiment tries to overcome the problem of delayed response to different mixture ratios, as discussed above.

Figure 2 shows a schematic overview of a third embodiment of the invention with a closed loop control system.

The control unit 14 measures via the sensor 13 the composition of the gas mixture. It compensates for deviations of a predefined composition by means of the proportional valves 11 and 12 at the gas inlets. This embodiment guaranties a quasi immediate response to a request to alter the mixing ratio. Pressure sensors at the inlets, to guard against a "no pressure" situation at the inlet are no longer necessary, since this must be the case if the controller is no longer able to obtain the requested gas composition. They may be, however, useful in order to build a more efficient controller unit.

Again, this embodiment can be placed before existing equipment for flow control or integrated into new equipment for flow control. It offers the advantages of improved reaction speed and size (no buffer volume needed) to the open loop control system.

It must be stated, however, the above given embodiments are extensively simplificated for reasons of clarity, and it is further possible to add some extra sensors for pressure measurement and flow measurement, and if the controller unit is well designed, this system can implement gas mixture and flow control all together, so no extra equipment for flow control will be necessary anymore.

Prevention of anoxemia and of the consequences of anoxemia have been investigated mainly in obstetrics, in cardiology and in transplant surgery. In obstetrics it is obvious that prevention of anoxemia and/or of the consequences of anoxemia are important to prevent brain damage of the child. Also in cardiology prevention of anoxemia and/or of the consequences of anoxemia as a result of ischemia is important to minimize the consequences of an infarction. During transplant surgery (kidney, heart, lung, liver) prevention of ischemia and/or anoxemia and/of of the consequences of ischemia and/or anoxemia is essential to minimize damage of the donor organ.

A lower temperature obviously decreases metabo-

lism and oxygen consumption and has been used to prevent ischemia and/or anoxemia e.g. for the mammary artery transplantation.

A cooled CO_2/oxygen mixture will be used to prevent adhesion prevention. The originality of the concept is illustrated by the recent introduction of 2 insufflators with warmed CO_2 up to 37°.

The invention further relates to methods for preventing adhesion by controlling anoxemia.

Claims

1. Use of an anoxemia preventing compound for the manufacture of a medicament for preventing adhesion formation.

2. Use according to claim 1, wherein the anoxemia preventing compound is chosen from:

   - activators of potassium channels;
   - modulators of macrophage activation and leucocyte attraction through cytokines, or their inhibitors;
   - the antibodies or inhibitors blocking the effect of VEGF expression;
   - indomethacin;
   - prostaglandin E1;
   - allopurinol;
   - calcium channel blockers;
   - free radical scavengers;
   - lipid peroxysomes;
   - pregnatrienes;
   - calcium antagonists;
   - prevention of hypoxia associated stress proteins;
   - acidosis;
   - MP;
   - dopamine;
   - ATP-$MgCl_2$;
   - O_2;
   - O_2 comprising gas mixtures;
   - O_2/CO_2 gas mixture.

3. Endoscopic insufflation system comprising gas supplying means for a insufflation line, **characterized** in that the supplying means are designed to supply gas mixtures comprising O_2.

4. Endoscopic insufflation system according to claim 3, **characterized** in that the gasmixture is a mixture of O_2/CO_2, in which gasmixture O_2 preferably is present in a volume ratio from 1 to 20% and more preferably from 5 to 20% and most preferably from 5 to 10%.

5. Endoscopic insufflation system according to claim 4, **characterized** in that the system comprises means for controlling the ratio O_2/CO_2 of the gas mixture.

6. Endoscopic insufflation system according to claim 4 or 5, **characterized** in that the system comprises means for controlling the flow rate of the O_2/CO_2 gas mixture.

7. Endoscopic insufflation system according to one of the preceding claims 3-6, **characterized** in that the system comprises means for moistening the insufflation gas.

8. Endoscopic insufflation system according to one of the preceding claims 3-7, **characterized** in that the system comprises means for the control of the temperature of the gas.

9. Method for preventing adhesion formation by preventing anoxemia.

10. Method according to claim 9, comprising administering to humans and animals in need of an adhesion preventing treatment a therapeutically effective amount of a compound chosen from:

    - activators of potassium channels;
    - modulators of macrophage activation and leucocyte attraction through cytokines, or their inhibitors;
    - the antibodies or inhibitors blocking the effect of VEGF expression;
    - indomethacin;
    - prostaglandin E1;
    - allopurinol;
    - calcium channel blockers;
    - free radical scavengers;
    - lipid peroxysomes;
    - pregnatrienes;
    - calcium antagonists;
    - prevention of hypoxia associated stress proteins;
    - acidosis;
    - MP;
    - dopamine;
    - ATP-$MgCl_2$;
    - O_2;
    - O_2 comprising gas mixtures;
    - O_2/CO_2 gas mixture.

11. Method according to claim 9 or 10, for preventing adhesion formation in endoscopy using a endoscopic insufflation system according to one of the claims 3-8.

12. Method according to claim 11, **characterized** in that the insufflating gas is a O_2/CO_2 gas mixture, in which gas mixture O_2 preferably is present in a volume ratio from 1 to 20% and more preferably from

5 to 20% and most preferably from 5 to 10%.

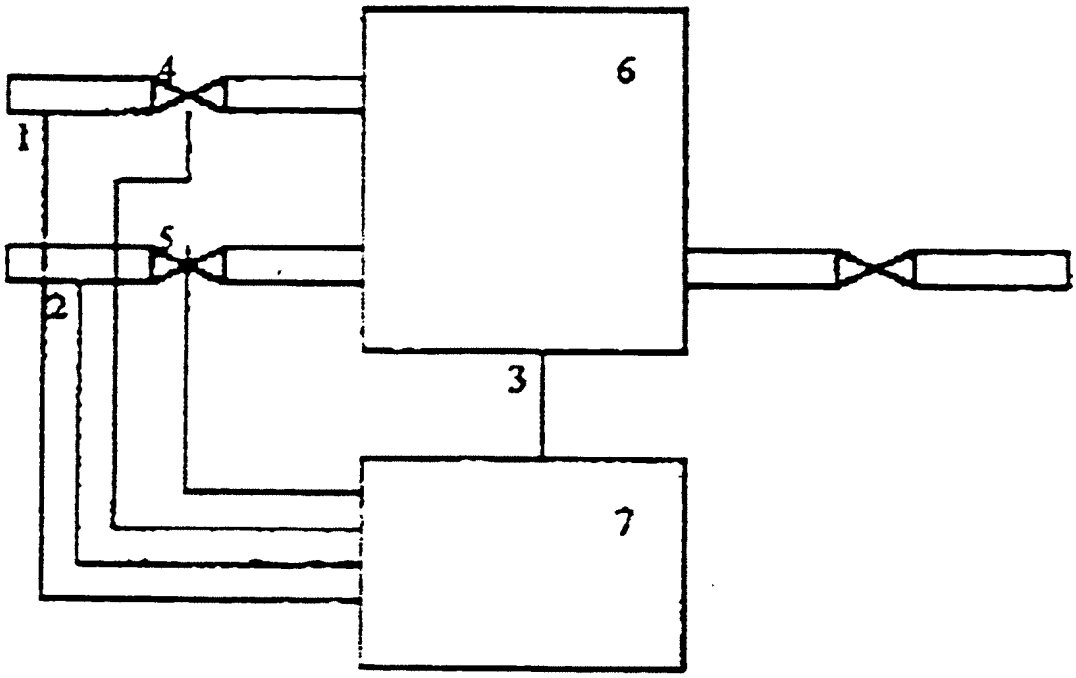

FIG. 1

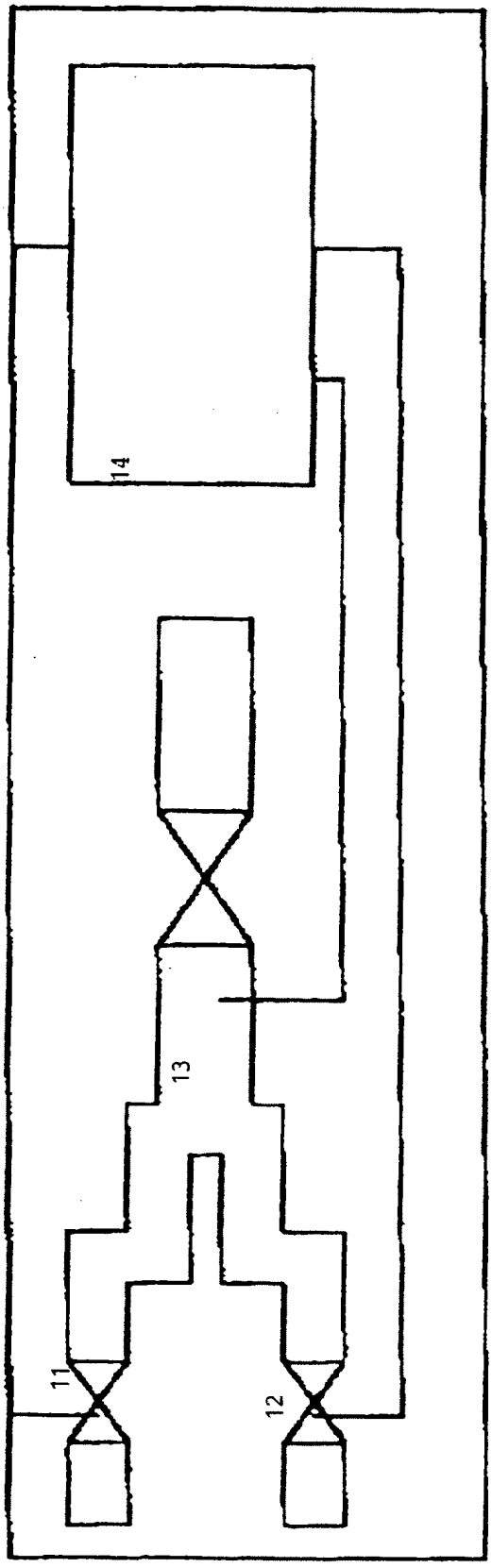

FIG. 2

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(72) Inventor: **The inventor has agreed to waive his entitlement to designation.**

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(57) The invention relates to an anoxemia preventing compound for the manufacture of a medicament for preventing adhesion formation.

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European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 97 20 1358

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
A	BAKKUM E.A. ET AL: "Postsurgical adhesion formation and prevention - Recent developments with regard to the consecutive stages in adhesion formation" REPRODUCTIVE MEDICINE REVIEW, 5/1 (37-49), March 1996, XP002041384 UNITED KINGDOM * page 37, right-hand column, paragraph 2; table 1 * ---	1,2	A61K31/00 A61K45/00 A61K31/405 A61K31/505 A61K31/557 A61K33/00 A61B1/00
A	LEGRAND EK ET AL: "Comparative efficacy of nonsteroidal anti-inflammatory drugs and anti-thromboxane agents in a rabbit adhesion-prevention model." J INVEST SURG, MAY-JUN 1995, 8 (3) P187-94, XP002041385 UNITED STATES * table 1 * ---	1,2	
A	DE LEON FD ET AL: "The prevention of adhesion formation by nonsteroidal antiinflammatory drugs: an animal study comparing ibuprofen and indomethacin." FERTIL STERIL, APR 1984, 41 (4) P639-42, XP002041386 UNITED STATES * page 641, left-hand column, last paragraph - right-hand column, paragraph 1; table 1 * ---	1,2	TECHNICAL FIELDS SEARCHED (Int.Cl.6) A61K
A	DESIMONE JM ET AL: "Indomethacin decreases carrageenan-induced peritoneal adhesions." SURGERY, OCT 1988, 104 (4) P788-95, XP002041387 UNITED STATES * the whole document * ---	1,2	
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The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
MUNICH	5 February 1999	Foerster, W

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P04C01)

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 97 20 1358

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
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A	STEINLEITNER A ET AL: "Calcium channel blockade prevents postsurgical reformation of adnexal adhesions in rabbits." OBSTET GYNECOL, NOV 1989, 74 (5) P796-8, XP002041388 UNITED STATES * the whole document *	1,2	
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A	STEINLEITNER A ET AL: "The use of calcium channel blockade for the prevention of postoperative adhesion formation." FERTIL STERIL, NOV 1988, 50 (5) P818-21, XP002041390 UNITED STATES * the whole document *	1,2	
A	USTUN C. ET AL: "The effects of Ringer's lactate solution and calcium channel blockers in the postoperative pelvic adhesion formation" DOGA TURK. J. MED. SCI., 1992, 16/10 (687-691), XP002041391 TURKEY * abstract *	1,2	

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TECHNICAL FIELDS SEARCHED (Int.Cl.6)

The present search report has been drawn up for all claims

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MUNICH	5 February 1999	Foerster, W

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EUROPEAN SEARCH REPORT

Application Number
EP 97 20 1358

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
Y	WO 97 00956 A (UNIV BOSTON) 9 January 1997 * page 3, line 22 - line 25 * * page 4, line 27 - page 5, line 13 * * page 8, line 3 - page 9, line 11 * * page 11, line 1 - page 13, line 15; claims 23,30,35 *	1,2	
Y	US 5 464 867 A (ANTANE MADELENE M ET AL) 7 November 1995 * column 5, line 45 - line 50 *	1,2	
A	US 5 411 988 A (BOCKOW BARRY I ET AL) 2 May 1995 * column 2, line 35 - line 43 * * column 4, line 1 - line 12 *	1,2	
A	US 5 407 426 A (SPEARS JAMES R) 18 April 1995 * the whole document *	1,2	
A	US 4 661 092 A (POPOVICH ROBERT P ET AL) 28 April 1987 * the whole document *	1,2	TECHNICAL FIELDS SEARCHED (Int.Cl.6)

The present search report has been drawn up for all claims

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& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P04C01)

European Patent Office

LACK OF UNITY OF INVENTION SHEET B

Application Number
EP 97 20 1358

The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

1. Claims: 1,2 (partially)

   Use of acitvators of potassium channels for the manufacture of a medicament for preventing adhesion formation.

2. Claims: 1,2 (partially)

   Use of modulators of macrophage activation and leucocyte attraction through cytokines, or their inhibitors for the manufacture of a medicament for preventing adhesion formation.

3. Claims: 1,2 (partially)

   Use of antibodies or inhibitors blocking the effect of VEGF expression for the manufacture of a medicament for preventing adhesion formation.

4. Claims: 1,2 (partially)

   Use of indomethacin for the manufacture of a medicament for preventing adhesion formation.

5. Claims: 1,2 (partially)

   Use of prostaglandin E1 for the manufacture of a medicament for preventing adhesion formation.

6. Claims: 1,2 (partially)

   Use of allopurinol for the manufacture of a medicament for preventing adhesion formation.

7. Claims: 1,2 (partially)

   Use of calcium channel blockers for the manufacture of a medicament for preventing adhesion formation.

8. Claims: 1,2 (partially)

   Use of free radical scavengers for the manufacture of a medicament for preventing adhesion formation.

9. Claims: 1,2 (partially)

European Patent Office

LACK OF UNITY OF INVENTION SHEET B

Application Number
EP 97 20 1358

The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

Use of lipid peroxysomes for the manufacture of a medicament for preventing adhesion formation.

10. Claims: 1,2 (partially)

Use of pregnatriens for the manufacture of a medicament for preventing adhesion formation.

11. Claims: 1,2 (partially)

Use of calcium antagonists for the manufacture of a medicament for preventing adhesion formation.

12. Claims: 1,2 (partially)

Use of prevention of hypoxia associated stress proteins for the manufacture of a medicament for preventing adhesion formation.

13. Claims: 1,2 (partially)

Use of acidosis for the manufacture of a medicament for preventing adhesion formation.

14. Claims: 1,2 (partially)

Use of MP (metalloproteins?) for the manufacture of a medicament for preventing adhesion formation.

15. Claims: 1,2 (partially)

Use of dopamine for the manufacture of a medicament for preventing adhesion formation.

16. Claims: 1,2 (partially)

Use of ATP-Mg2Cl2 for the manufacture of a medicament for preventing adhesion formation.

17. Claims: 1,2 (partially)

Use of O2, O2 comprising gas mixtures and O2/CO2 gas mixtures for the manufacture of a medicament for preventing

European Patent Office

LACK OF UNITY OF INVENTION SHEET B

Application Number
EP 97 20 1358

The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

adhesion formation.

18. Claims: 3-8

Endoscopic insufflation system

European Patent Office

INCOMPLETE SEARCH
SHEET C

Application Number
EP 97 20 1358

Claim(s) searched completely:
1,2 (partially as far as subject 1)

Claim(s) not searched:
9-12

Reason for the limitation of the search (non-patentable invention(s)):

Article 52 (4) EPC - Method for treatment of the human or animal body by surgery or therapy

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Further limitation of the search

Claim(s) searched completely:
1 (partially as far as subject 1

Claim(s) searched incompletely:
2

Reason for the limitation of the search:

The following definitions in claim 2 are lacking clarity: " acidosis" as compound and "MP".

ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 97 20 1358

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